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Some observations on the epidemiology and transmission of hepatitis B

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Introduction

Although jaundice was described in the medical writings of Mesopotamia during the Babylonian period, progress in the understanding of infectious hepatitis did not occur until the second world war. Investigations carried out during outbreaks of jaundice in the armed Forces led to the establishment of the viral aetiology of the disease and also confirmed that there were two distinct epidemiological and immunological forms (Von Voegt, 1942; Cameron, 1943). Later the parenteral spread of hepatitis B was clearly established in clinics for the treatment of venereal diseases, diabetic clinics, and antituberculosis dispensaries and was shown to be associated with the repeated use of inadequately sterilised needles and syringes.

The virus believed to be responsible for this type of hepatitis, characterised by a long incubation period and parenteral transmission, was termed hepatitis B virus to distinguish it from the virus responsible for classical, short-incubation, infectious hepatitis known as hepatitis A virus. Since the discovery of the Australia antigen and its association with hepatitis B by Blumberg (1964 and 1968) there has been a tremendous increase in knowledge about both viruses and their associated antigens. A recent World Health Organisation Expert Committee (1976) has suggested standardisation and improvements in nomenclature.

Hepatitis B virus

The hepatitis B virus (HBV) is a 42-nm double-shelled virus and was formerly known as the Dane particle (Dane *et al.*, 1970). HBV has at least three separate antigens. These are now called hepatitis B surface antigen (HbsAg), hepatitis B core antigen (HbcAg), and hepatitis B e antigen (HbeAg).

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HEPATITIS B SURFACE ANTIGEN

HbsAg is found on the surface of the virus and can also be demonstrated on the small spherical particles and tubular forms found with the Dane particle. It is said to display antigenic heterogenicity because, in addition to the common determinant 'a', HbsAg particles also have two type-specific subdeterminants, either d or y and either w or r. The importance of this heterogenicity lies in the existence of virus subtypes, because infection with one virus subtype may fail to produce immunity to another subtype. The heterogenicity has been of value in epidemiological studies, and it is probable that further subtypes exist. The antibody to HBsAg is known as anti-Hbs.

HEPATITIS B CORE ANTIGEN

The term hepatitis B core antigen (HbcAg) is used for the antigen present in the core of the Dane particle and can be demonstrated only after disruption of the outer membrane of HBV. It has not been found in the blood but can be detected in the nuclei of infected hepatocytes. Its corresponding antibody is designated anti-Hbc.

HEPATITIS B e ANTIGEN

The third antigen associated with HBV is designated e and has two subtypes HbeAg/1 and HbeAg/2. There is a definite association between the presence of HBeAg in HbsAg-positive serum and the presence of Dane particles or HBV. The detection of HbeAg appears to be an accurate marker of a high degree of infectivity in patients with HbsAg-positive serum.

Interpretation of serological results

After a patient is infected with hepatitis B virus, HbsAg and HbeAg may be found in the serum for approximately four weeks before the onset of symptoms. Once symptoms and signs have developed HbsAg starts to decline in titre and disappears within about six weeks. The normal antibody to HbsAg, anti-Hbs, does not appear until convalescence and is frequently at a low titre.

HbeAg is cleared from the blood more rapidly, and its disappearence is associated with the appearance of anti-Hbe. HbcAg has not been demonstrated in the blood yet, but the antibody anti-Hbe is present even earlier than anti-Hbs, usually at about the time of the rise in the serum aminotransferases. It probably remains in the serum for only a short time and its presence is often taken as evidence of recent infection with HBV.

If the clinical course of long-incubation hepatitis does not proceed to resolution and recovery, changes may occur in the immune responses which help the clinician to identify such cases. When acute hepatitis B progresses to chronic hepatitis HbsAg and HbeAg persist in the serum beyond 13 to 15 weeks. This is likely to occur in about 5% of patients and suggests that the patient is not producing sufficient antibodies of high affinity to eliminate the virus (Nielson *et al.*, 1971). However, in the rarer cases of fulminant hepatitis B HbsAg usually disappears rapidly from the serum, indicating an enhanced antibody response.

Methods of transmission

Epidemic hepatitis A is usually caused by drinking contaminated water or eating shellfish containing the virus. Sensitive serological tests for the diagnosis of infection by both hepatitis B virus and hepatitis A virus show that while the former is increasing in frequency, especially among men, the latter has shown a progressive decline. It has now become obvious that some episodes of acute viral hepatitis are not due to either of these viruses or to other potential liver pathogens, such as the Epstein-Barr virus or cytomegalovirus. In some hospitals what is called non-A non-B hepatitis is the commonest form occurring after blood transfusions. It has been suggested that the same viruses may be responsible for transfusion hepatitis and sporadic cases, but there are not yet any suitable tests for detecting them.

Since the second world war hepatitis B has been believed to result principally from parenteral inoculation of human blood products containing the virus. The principal blood products concerned were human immune sera, vaccines containing human serum, plasma, blood for transfusion, and, in addition, inadequately sterilised syringes, needles, scalpels, other surgical and dental instruments, ear-piercing equipment, tattooing needles, and acupuncture needles. Considerable evidence has recently accumulated to suggest that hepatitis B is frequently transmitted by non-parenteral routes. For example, the almost universal adoption of disposable syringes and needles in Europe and North America has made this method of transmission uncommon, and it is now virtually limited to drug addicts. The discovery of sensitive tests for the antigens of hepatitis B has made it possible to screen all blood products before they are administered to patients, and further precautions are taken to protect doctors, nurses, and laboratory workers.

Despite measures to reduce the risk of contamination the prevalence of hepatitis B has not decreased, and in Europe and the United States it is actually increasing relative to hepatitis A. It was, therefore, essential to re-examine the epidemiology of hepatitis B, as in the majority of sporadic cases there was no history of parenteral exposure to the virus. For example, Prince *et al.* (1970) found in New York State that 55% of adult patients with hepatitis and hepatitis B antigen-positive sera gave no history of recent blood transfusions, inoculations, self-administered intravenous drugs, tattooing, acupuncture, or other possible parenteral exposure. Occasional reports at this time suggested that in some cases infection might be passed between sexual partners, but there was no evidence to suggest that sexual transmission was important in maintaining the prevalence of the disease in the general population.

Sexual transmission

In 1973 several studies were reported from London (Fulford *et al.*, 1973; Heathcote and Sherlock, 1973; Jefferies *et al.*, 1973) describing the relationship of sexual practices and infection with hepatitis B virus. For example, our own investigation at the Middlesex Hospital (Fulford *et al.*, 1973) showed that the frequency of HbsAg and its antibody was 10 times greater in the sera of patients attending the clinic for sexually transmitted diseases than in a control group of blood donors attending a blood transfusion centre in north London. The antigen-positive patients were predominantly male homosexuals, and a marked correlation was found between positive results and a history of other sexually transmitted diseases, notably syphilis and gonorrhoea. Repeated homosexual exposure and promiscuity increased the probability of the patients having positive results, and it seemed probable that many of the homosexual patients attending the clinic had at some time been infected with the virus.

The frequency of drug abuse was low in this group of patients and careful history taking made it unlikely that parenteral transmission was a possible cause of infection; nor was there any evidence that infestation with lice and scabies might be responsible. It was concluded that there was strong circumstantial evidence that the virus of

hepatitis B could be sexually transmitted and that this might be one of the commoner methods of spread of the agent in Britian today.

These conclusions were supported by the work of Jefferies *et al.* (1973) in London and Szmuness *et al.* (1975) in New York. They each tested over 1000 patients attending venereal diseases departments and found hepatitis B antigen and antibody 10 times more frequently in the patients than in controls. In both studies the great majority of the positive patients were homosexual men.

Heathcote and Sherlock (1973) reported details of a survey of 67 patients admitted to hospital with acute hepatitis B. They concluded that sexual or domestic contact was the most likely source of infection in 27 (40%) patients. Two further studies carried out at the departments of genitourinary medicine and virology at the Middlesex Hospital have confirmed these findings (Lim *et al.*, 1976 and 1977). The strong association between the presence of antibodies and homosexuality was confirmed. Thirty per cent of homosexual or bisexual men were antibody-positive compared with 5% of heterosexual men. The presence of antibody was associated with an increased number of sexual partners and with the practice of anorectal intercourse. There was also an association between antibody and orogenital sexual contact. HbsAg has been demonstrated in the saliva, seminal fluid, and vaginal secretions, especially when it is present in high concentrations in the serum, and these findings suggest several possible mechanisms of spread during sexual activity, although concentrations in these body secretions are always much lower than in the blood.

In all our previous studies it had been noted that overt clinical hepatitis was relatively uncommon. In one of our recent series of 29 men found to be antibody-positive, only seven gave a history compatible with past hepatitis. It seems probable that in sexually acquired hepatitis B the acute stage of the disease is often mild and subclinical. This is well known in transfusion-associated hepatitis where anicteric hepatitis occurs two or three times more frequently than overt hepatitis (National Transfusion Hepatitis Study, 1972). Anicteric hepatitis B could be of importance in the pathogenesis of chronic liver disease, as chronic sequelae are frequently observed following hepatitis B infection in immunosuppressed patients, in whom the illness tends to be milder, may be anicteric, and is of longer duration. It could also be of great importance in the development of the chronic carrier state.

The carrier state

Recently a small group of 10 homosexual men with evidence of chronic type B hepatitis and persistent HbsAg at a high titre in their sera were investigated in detail, and special efforts were made to trace their sexual contacts and examine them. Many of these men were highly sexually active and had numerous casual sexual contacts, the majority of whom were completely untraceable. Nevertheless, they had in addition some regular partners and were very co-operative in arranging for them to attend the department.

All these 10 men, diagnosed as having chronic type B hepatitis, had liver disease for more than one year and in several instances for more than five years. Several of them had no clear-cut history of an acute attack of hepatitis or of jaundice, and their infections were probably subclinical and mild. Biochemical tests of liver function were either normal or only mildly abnormal, usually in the form of fluctuating serum transaminase concentrations. HbsAg was present at high titres in the sera of all the patients, usually at a titre of 1/10 000 or higher by the reverse passive haemagglutination test.

HbeAg is usually believed to be associated with the presence of Dane particles or hepatitis B virus and therefore with infectivity. All our patients with chronic hepatitis had e antigen in their sera. The majority also had subtype Ad antigen, which is the predominant subtype found among British-born blood donors. Subtype Ay is the predominant subtype in drug addicts in Western countries and also in patients and carriers from the Middle East and Mediterranean countries.

These chronic, high-titre HbeAg carriers appear to be in a stable state when followed up over a period of several years, and there is every indication that they may remain infectious for periods of up to 10 years or longer. The titre of HbsAg in their serum usually remains at a high level, frequently in the region of 1/10 000, although in some patients we have noted a gradual fall in titre.

In contrast the acute cases of hepatitis in whom jaundice developed usually recovered rapidly and completely. HbsAg was present in their sera at relatively high titres when the diagnosis was made, but the titre of antigen fell rapidly and disappeared within about three months of the onset of the disease. These patients are probably only highly infectious sexually for a few weeks, and in the majority the prognosis is excellent. Their opportunities for infecting sexual partners are probably very small when compared with the chronic carriers

who remain, as far as we can tell, infectious for many years.

From this investigation there has emerged the picture of a particular type of sexually active homosexual man who may be of vital importance in maintaining the high incidence of hepatitis B in the male homosexual population. He has had symptomless hepatitis B in the past, is usually subjectively well, sometimes has a palpable liver, and has a high titre of HbsAg, frequently of the order of 1/10000 or more. His serum will show the presence of HbeAg and the subtype will be Ad. He may also have HbsAg in his saliva and seminal fluid, usually at a low titre. He may remain in this stable state for many years, and during this time he is probably infectious to his homosexual sexual partners.

There have been similar situations in the epidemiology of infectious diseases in the past, and almost every medical student and doctor remembers the story of Mary Mallom, a symptomless cook, who spread typhoid fever widely in New York State during the early years of this century. Even after the source of the infection was traced to her and she had been placed in preventative detention, she escaped and again got work as a hospital cook, infecting a further 23 people before she was apprehended. Her story became so well known that she was universally known as 'Typhoid Mary'.

Because of the similarities between the epidemiological facts we should like to suggest that homosexual men who are chronic carriers of the HBV and remain infectious for a prolonged period should in future be known as 'Hepatitis Harolds', after the name of the first patient in whom the carrier state was fully established. This name might help to identify these highly infectious individuals and ensure that they are warned that they are infectious to their sexual partners. 'Hepatitis Harolds' are characterised by the following features:

1. Homosexuality.
2. HbsAg at high titres.
3. e antigen-positive.
4. Subtype Ad.
5. No definite history of acute hepatitis.
6. Sometimes palpable liver.
7. Stable state for many years.
8. Infectious to homosexual partners for long periods of time.

Contact tracing and epidemiological studies have demonstrated how easily the condition is spread to other men, particularly among the promiscuous homosexuals. Only a few of the contacts will develop jaundice and clinically recognisable acute hepatitis. A significant number will remain symptomless, and some new chronic carriers will emerge. However, despite full co-operation from the patients a complete picture of all the men at risk cannot be obtained because of the casual nature of much of the homosexual activity.

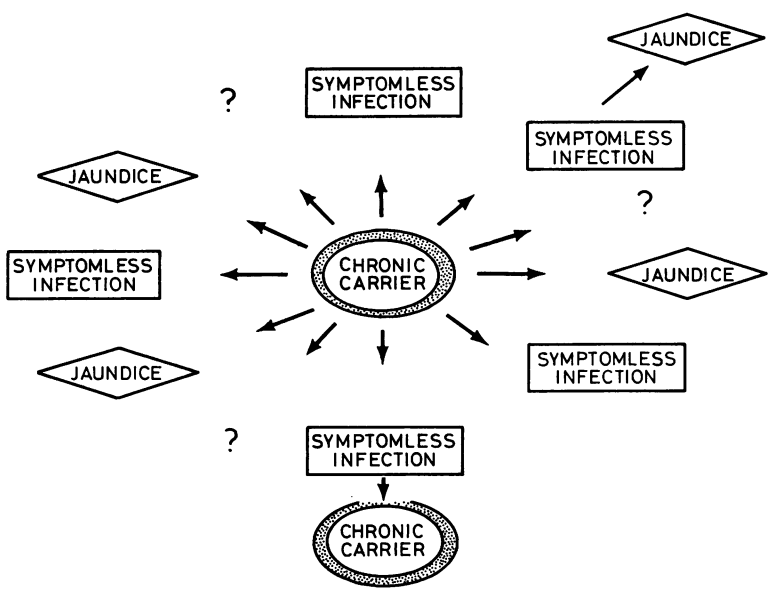

Figure *Spread of hepatitis B from a chronic homosexual carrier*

Our experience suggests that the sexual transmission of HBV is not particularly common among heterosexual people in the United Kingdom. Nevertheless, there is good evidence that some men, who are chronic carriers of HbsAg and are HbeAg-positive, are highly infectious to their female sexual partners. We have studied three such men, each of whom has infected three or more female sexual partners. There is much less evidence that women who are chronic carriers infect their male sexual partners, although the difference between homosexuals and heterosexuals may simply be due to the fact that many homosexual men have a much greater number of sexual contacts. There may also be some factor concerned with the type of sexual practices of homosexual men that makes the transfer of the virus of hepatitis B more likely, although no positive evidence of this has emerged in any of our investigations.

Discussion

There now appear to be two well established ways by which HBV is maintained in the community in the United Kingdom: homosexual men of the 'Hepatitis Harold' type, who are chronic carriers of HbsAg and are also positive for HbeAg and may well be responsible for the majority of sexually transmitted cases; and drug addicts, who may also be highly infectious, long-term carriers—only in this instance they would be infected with subtype Ay. The older, more classical means of transmission, such as transfusions and working with blood products and unsterilised instruments, may not now contribute greatly to the number of infected persons.

If the level of hepatitis B virus in the community is more dependent on the comparatively few chronic HbeAg-positive carriers in homosexual and drug addict circles than on acute infections it could in all probability be considerably reduced by identifying all the chronic carriers. For this to be possible a simple, specific, and sensitive screening test is required so that the sera of those in high risk groups, such as patients attending clinics for sexually transmitted diseases and those seen at drug-addiction clinics, could be tested. Those who were found to be chronic infectious carriers could be warned that they are infectious to their sexual partners and could be kept under observation to see whether they eventually became non-infectious.

Although simple screening of serum for HbsAg could do much to control the spread of hepatitis B, the development of a safe and effective vaccine for people who are at risk of acquiring the infection would be a major step forward. However, it is not yet certain that anti-Hbs is a protective antibody, and further development of this approach will depend on the establishment of this fact and on the ability to produce a safe preparation containing only completely inactivated virus which is free from the dangers of harmful immunological reactions.

Preparations of gamma globulin containing high titres of anti-Hbs (hyperimmune globulin) are available and have been used prophylactically. However, the degree of protection and the long-term effects of their administration are unknown. Nevertheless, they are probably the most effective treatment available to protect against a single, known exposure, and supplies are available from the director of the local public health laboratory services. Supplies are limited, and it is not yet possible or desirable from the point of view of safety to make this treatment available to all men who have had homosexual intercourse with a known chronic carrier.

Eventually treatment of acute hepatitis B with anti-viral agents may be developed. Treatment of chronic infectious carriers might either reduce their infectivity or make them completely non-infectious, but developments in this aspect of the disease must await solutions to the production problems with interferon and interferon-inducers or the development of new and effective anti-viral agents.

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